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## Spray drying of cubosomes for oral vaccine delivery

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**PURPOSE:** To prepare cubosomes encapsulated with the model antigen ovalbumin via spray drying, and to characterize such cubosomes with a view for their potential application in oral vaccine delivery.

**METHODS:** Cubosomes consisting of the lipid dimodan, loaded with ovalbumin as a model antigen and with a surrounding dextran shell were prepared. Dimodan dissolved in ethanol (1.78 w/v%) was first mixed with a solution of ovalbumin in water (0.075 final w/w% of ovalbumin). After 1 h of mixing, dextran dissolved in water (1.77 w/v%) was added to the lipid/ovalbumin solution (0.72 w/w% of lipid + ovalbumin), and the final solution was spray dried on a Büchi mini spray dryer. Cryo-TEM was utilized to identify the cubic phase of the spray dried product. To confirm the cryo-TEM results, SAXS experiments were performed on a SAXS/WAXS beamline at the Australian Synchrotron. Hydrated cubosomes were enclosed in glass capillaries and 2D SAXS patterns were collected. The size of cubosomes coated with dextran was measured using time-of-flight mass spectrometry, whereas dynamic light scattering was used to measure the size of the cubosomes dispersed in water (with no dextran shell). The amount of loaded ovalbumin was measured by dissolving cubosomes in PBS containing 5% Triton X-100 followed by application of the BCA assay, while the release of ovalbumin from the cubosomes was investigated on a  $\mu$ -Diss profiler (Pion Inc.) with PBS pH 6.5 as the release medium over a period of 97 h.

**RESULTS:** The spray drying process resulted in the formation of cubosomes as verified by cryo-TEM, where the cubic phase of the particles was identified (Figure 1). The presence of the cubic phase was also confirmed by the use of SAXS, where the cubic phase could be identified after hydration of the particles. Cubosomes with a dextran shell had a size of  $1.33 \pm 0.13 \mu\text{m}$ , whereas the dispersed cubosomes was found to have a size of  $282 \pm 7 \text{ nm}$  (PDI = 0.18). Approximately 85  $\mu\text{g}$  of ovalbumin was found to be entrapped in 1 mg of cubosomes resulting in a loading of ovalbumin of approximately 8.5%. Release studies showed that during the first 70 h the ovalbumin was released slowly, followed by a more rapid release from 70-80 h. A total release of  $47.9 \pm 2.8 \%$  was seen over the 97 h period in relation to the total loading of ovalbumin in the cubosomes (Figure 2).

**CONCLUSIONS:** The spray drying process resulted in the formation of cubosomes with encapsulated ovalbumin and surrounded by a dextran shell. The cubosomes will be further developed for oral vaccine delivery with the future perspective of filling the cubosomes into polymeric microcontainers – this is made possible due to the dextran shell of the particles. Such microcontainers offer the possibility to protect the cubosomes during passage through the stomach, and to provide a release of the cubosomes from the microcontainers in the small intestine.

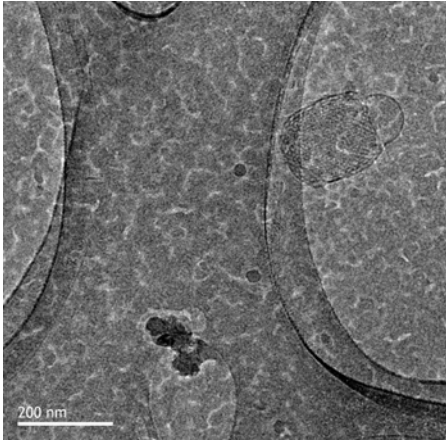


Figure 1: Cryo-TEM of the cubic phase of the spray dried particles produced from dimodan

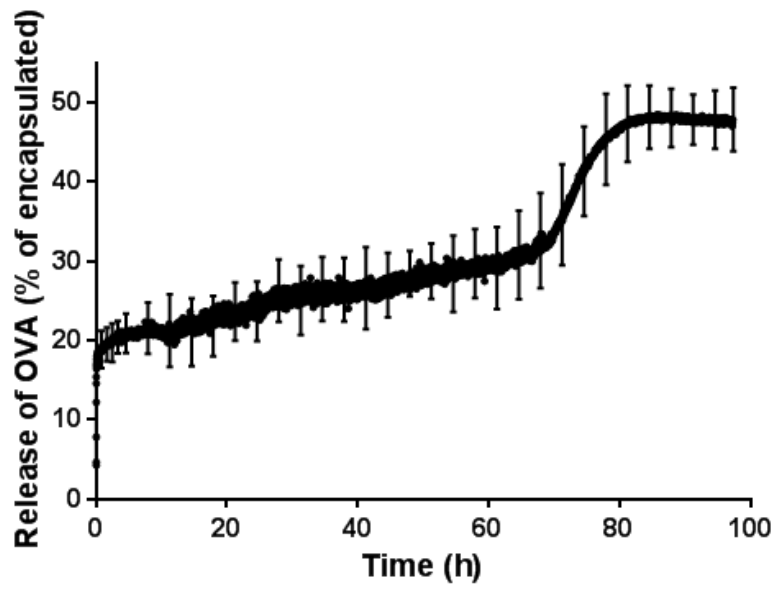


Figure 2: Release of ovalbumin from dimodan cubosomes, expressed as % of total incorporated ovalbumin.